

REVIEW TOPIC OF THE WEEK

Isolated Noncompaction of the Left Ventricle in Adults



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ABSTRACT

Isolated left ventricular noncompaction (ILVNC) is a cardiomyopathy that was first described in 1926 as a “spongy myocardium.” The disorder results from intrauterine arrest of compaction of the loose interwoven meshwork of the fetal myocardial primordium and subsequent persistence of deep trabecular recesses in the myocardial wall. The classical clinical presentation is a triad of heart failure, arrhythmias, and embolic events from mural thrombi. ILVNC has been associated with several autosomal dominant, X-linked, and mitochondrial genetic mutations that are also shared among other cardiomyopathies. Over the past decade, ILVNC has been subject to intensive research, as it increases the risk for sudden cardiac death. This review focuses on the current understanding of ILVNC in adult populations and attempts to provide organized insight into the disease process, screening, diagnosis, management, role of device therapy, and prognosis. (J Am Coll Cardiol 2015;66:578–85) © 2015 by the American College of Cardiology Foundation.

Isolated left ventricular noncompaction (ILVNC) is a rare cardiomyopathy classified as a primary genetic cardiomyopathy by the American Heart Association (1). It is still considered unclassified in the European Society of Cardiology classification (2), as it remains unclear whether it represents a distinct disease process or a morphological trait shared by many phenotypically different cardiomyopathies.

ILVNC results from intrauterine arrest of compaction of the loose meshwork of the fetal myocardial primordium (3,4) and subsequent persistence of deep trabecular recesses in the myocardial wall. The first pathological description of spongy myocardium dates back to 1926 (5). However, ILVNC was first designated as a clinical entity in 1984, identified by the isolated persistence of “sinusoids” in the left ventricle (6), which communicate with the left ventricular cavity and are usually filled with blood from the ventricle. Note that if noncompaction is concomitantly present with other structural abnormalities (i.e., hypertrophic cardiomyopathy), the diagnosis of “left ventricular

noncompaction in association with” is more appropriate (7).

ILVNC has gained increasing attention (1,2) because of its association with high rates of mortality and morbidity in adults, including heart failure, thromboembolic events, and tachyarrhythmias (8). Paradoxically, its prognosis appears better when identified early in childhood (9). This review focuses on the current understanding of ILVNC in the adult population and provides an illustrative portrayal of the disorder.

EMBRYOLOGY

During embryogenesis, the myocardium consists of a loose network of interwoven fibers separated by deep intertrabecular recesses linking the myocardium with the left ventricular cavity. Between the fifth and eighth weeks of embryonic development, this meshwork compacts, proceeding from the epicardium to the endocardium and from the base of the heart to the apex (3,10–12). Ventricular noncompaction results

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from intrauterine arrest of this process, due to pressure overload or myocardial ischemia preventing the normal compaction process and regression of the myocardial sinusoids (8).

Although noncompaction of the myocardium is seen in association with other congenital cardiac abnormalities (Table 1), it can also occur as a primary disorder in the absence of other structural heart disease (7). This latter circumstance, referred to as ILVNC, is the topic of this review.

PREVALENCE

The true prevalence of ILVNC is difficult to determine because diagnostic criteria are not standardized. Most studies addressing this issue are from tertiary medical centers and performed in populations with symptoms or abnormal physical examination findings and for family screening of patients with the disorder (8,9,13-15). Therefore, a major limitation is that available prevalence data are derived from retrospective databases fraught with selection biases. In a report from Switzerland, only 0.014% of patients undergoing echocardiography between January 1984 and December 1998 were identified as ILVNC cases (8). However, in the past decade, increased awareness of the disorder, as well as improvements in echocardiographic image acquisition and processing, have led to greater detection. Thus, the Swiss study is likely to have underestimated disease prevalence. ILVNC is significantly more prevalent within the heart failure population (16,17), which is not surprising, as heart failure remains its most classical presentation.

GENETICS

ILVNC is a genetically heterogeneous disease that can be either familial or sporadic. Familial recurrence appears more commonly in adults with ILVNC (18) than in children (19) and may be autosomal dominant, X-linked, or mitochondrial in origin. The recurrence of noncompaction phenotypes in families varies between 18% and 50% (8,20,21). Although retrospective designs limit their general applicability, prior studies suggest that a detailed pedigree analysis of patients presenting with ILVNC is warranted. It is also generally recommended that asymptomatic relatives of affected individuals be screened using echocardiography (22).

Table 1 describes the major gene mutations associated with LVNC that overlap with other cardiac disorders. Notably, mutations in the sarcomeric cardiac beta-myosin heavy chain gene (MYH7), previously linked with hypertrophic cardiomyopathy, restrictive cardiomyopathy, and dilated cardiomyopathy, have been identified in 2 families with ILVNC (23), suggesting potential overlap among cardiomyopathy genes (23-35).

Despite the major advances noted earlier, the precise correlation between genotype and phenotypic expression in cardiomyopathies is poorly understood. Available data suggest that, for certain mutations, noncompaction and hypertrophic, restrictive, and dilated cardiomyopathies are not clearly distinct entities (26,27). In summary, the currently available genetic data suggest significant genetic heterogeneity in ILVNC, and the major genetic cause for familial

ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance
ICD = implantable cardioverter-defibrillator
ILVNC = isolated left ventricular noncompaction
NYHA = New York Heart Association

TABLE 1 Major Gene Mutations Associated With LVNC and Their Overlap With Other Cardiac Disorders

Disorder	TAZ-G4.5 Mutation	DTNA Mutation	Z-Band Mutation	FKBP12 Mutation	LMNA Mutations	NKX2.5, TBX5, CSX Mutations	ACTC, TNNT2, MYH7 Mutation	SCN5A Mutation	HCN4 Mutation
LVNC	×	×	×	×	×	×	×	×	×
Ventricular/atrial septal defect		×		×		×			
Arrhythmogenic right ventricular cardiomyopathy				×					
Dilated cardiomyopathy	×		×	×	×		×		
Hypertrophic cardiomyopathy							×		
Other cardiomyopathies*	×		×			×		×	
Other conduction abnormalities†					×	×	×	×	×
Tetralogy of Fallot						×			
Ebstein anomaly						×			
Brugada syndrome								×	
Romano-Ward syndrome								×	

*X-linked infantile cardiomyopathy, X-linked endocardial fibroelastosis, hypoplastic left heart syndrome. †Bundle blocks, atrioventricular nodal blocks, tachyarrhythmias, bradyarrhythmias. ACTC = alpha-cardiac actin (24); CSX = cardiac specific gene located on 5q (65,66); DTNA = alpha-dystrobrevin gene, transition C to T mutation, located on 18q12 (19); FKBP12 = responsible for release of calcium from sarcoplasmic reticulum via ryanodine receptor (67); HCN4 = hyperpolarization-activated cyclic nucleotide channel 4 (68); LMNA = Lamin A/C related sequence located on 1q22 (69); LVNC = left ventricular noncompaction; MYH7 = B-myosin heavy chain (23-25); NKX2.5 = homeobox protein located on chromosome 5 (65,66); SCN5A = human cardiac sodium channel alpha-subunit gene (70); TAZ-G4.5 = encodes tafazzin located on Xq28, (18,19,71); TBX5 = T-box transcription factor located on chromosome 12 (65,66); TNNT2 = cardiac troponin T (24); ZASP = Z-band alternatively spliced PDZ motif-containing protein on 10q22.2-q23.3 (72).

noncompaction remains to be identified. Genetic testing has not yet yielded improvements in clinical management of patients but may provide insight as to the underpinning of ILVNC.

PRESENTATION

ILVNC is characterized by a wide spectrum of presentations and variable outcomes (28). It is commonly discovered through screening of family members of affected patients during early, nonsymptomatic stages (28). Among symptomatic patients, the triad of heart failure, arrhythmias, and embolic events (3,8,10,11) is the most classical presentation, particularly for patients with reduced left ventricular systolic function (3,29).

In practice, most ILVNC cases are diagnosed in patients presenting with unexplained heart failure. The clinical symptoms are usually related to systolic or diastolic dysfunction; however, nonspecific symptoms and/or arrhythmias may be present initially (8,9,11,13-15,21,22,28,30). Despite increased awareness, there is still a significant delay in establishing the correct diagnosis, with a mean time from symptom onset of ~3.5 years, although this is likely to have improved with recent advances in echocardiography.

In a case series by Chin *et al.* (11), left ventricular systolic dysfunction was present in up to 60% of patients. According to the investigators, subendocardial hypoperfusion and microcirculatory dysfunction may serve as the etiology for both systolic ventricular dysfunction and arrhythmogenesis. Subendocardial perfusion can be abnormal, despite the absence of coronary artery disease (11), and is believed to result from isometric contraction of the endocardium and myocardium within the deep intertrabecular recesses.

Diastolic dysfunction, likely the result of restricted filling due to the numerous, prominent trabeculae, is ubiquitous in ILVNC (10). Initial presentation of ILVNC as a restrictive cardiomyopathy has been reported in children (21,31), but not in adults.

In a Swiss cohort that was 74% male, reasons for referral included heart failure (62%), abnormal echocardiographic findings (12%), and palpitations (6%) (8). Presenting symptoms included dyspnea in 79% (65% New York Heart Association [NYHA] functional classes I and II, 35% NYHA functional classes III and IV), chest pain (26%), and atrial fibrillation (26%). The mean left ventricular ejection fraction was 33%, and 94% of patients had an abnormal electrocardiogram (the most common abnormality was left bundle branch block, observed in ~44%). Although embolic events were not a reason for referral in this series, they are a common complication.

The largest pediatric series (11,21) reported associated facial dysmorphism (prominent forehead, low-set ears, strabismus, high-arching palate, and micrognathia) and Wolff-Parkinson-White syndrome. These are generally not present in adult cases and are likely explained by differing genetics.

The anatomic distribution of ILVNC in pediatric patients and adults is similar: most commonly apical, followed by midventricular (midinferior and midlateral segments) and then basal segments. No septal involvement was noted in a pediatric cohort of 15 patients (32), with the number of affected segments being the strongest predictor of systolic dysfunction.

Although most noncompaction is believed to be congenital, Finsterer *et al.* (33,34) suggested that ILVNC can be acquired. In their case series, patients had previously normal echocardiograms. Most had coexistent neuromuscular disorders and mitochondrialopathies, similar to the congenital form. There are also a few case reports of ILVNC resulting from intense athletic training (35) or as an adaptive mechanism of an impaired myocardium, such as ischemic heart disease or trauma (36,37). In a retrospective review of acquired noncompaction, the average detection time from a previously normal echocardiogram was 3.8 years (38).

DIAGNOSIS

Diagnosis of ILVNC is often delayed due to failed recognition. The absence of a consensus on absolute diagnostic criteria is a contributing factor. Resting electrocardiogram abnormalities are found in most patients, but findings are nonspecific and include left ventricular hypertrophy, repolarization changes, inverted T waves, ST-segment changes, axis shifts, intraventricular conduction abnormalities, and atrioventricular blocks (3,8,11,21). Arrhythmias are common, including ventricular tachyarrhythmias, atrial fibrillation, and paroxysmal supraventricular tachycardia, all of which can precipitate sudden death (3,8,11).

Two-dimensional echocardiography with color Doppler is the study of choice for diagnosis and follow-up of ILVNC. Proposed echocardiographic criteria for ILVNC include (7):

- Absence of coexisting cardiac abnormalities;
- Segmental thickening of the left ventricular myocardial wall, consisting of a thin compacted epicardial layer and a thickened endocardial layer with prominent trabeculations and deep recesses;
- Noncompaction to compaction ratio ≥ 2 at end-systole (Central Illustration);

- Predominant localization of pathology in the mid-lateral, apical, and midinferior regions of the left ventricle (Figure 1); and
- Color Doppler evidence of deep, perfused inter-trabecular recesses.

Frischnecht et al. (39) validated these criteria against idiopathic dilated cardiomyopathy and cardiomyopathy related to valvular or hypertensive heart disease. Kohli et al. (40), however, argue that these criteria may be too sensitive, lacking specificity for noncompaction. No consensus exists on their validity, although the specificity seems likely to be greater than using the noncompaction/compaction ratio alone. Similarly, if segments other than those mentioned in the diagnostic criteria are involved, ILVNC is unlikely. Note that the morphological description of abnormal trabeculae varies depending on the echocardiography planes and the phase of the cardiac cycle in which these are obtained (40). Prominent trabeculations should be recognized as a common variant of normal hearts; this remains an important diagnostic consideration and clinical dilemma. In normal hearts, however, trabeculations most often course from the free wall to the inter-ventricular septum, whereas in ILVNC, trabeculations spare the septum (41). The use of contrast echocardiography (42) and Doppler tissue (strain rate) imaging (43) can help to further clarify the diagnosis.

Cardiac magnetic resonance (CMR) imaging is increasingly used in clinical practice to describe myocardial morphology and can be extremely useful in confirming the presence of left ventricular non-compaction (42,44,45). CMR serves a particularly important role for patients in whom adequate echocardiographic imaging cannot be obtained (Figure 2). In this setting, transesophageal echocardiography can also be performed (46).

Two-dimensional CMR measurements adapted from echocardiographic criteria are similarly limited. André et al. (47) noted that between 26% and 70% of healthy volunteers, depending on age and sex, fulfilled the 2-dimensional CMR criteria for a non-compaction diagnosis. Therefore, 3-dimensional CMR is deemed more appropriate for developing quantitative diagnostic criteria.

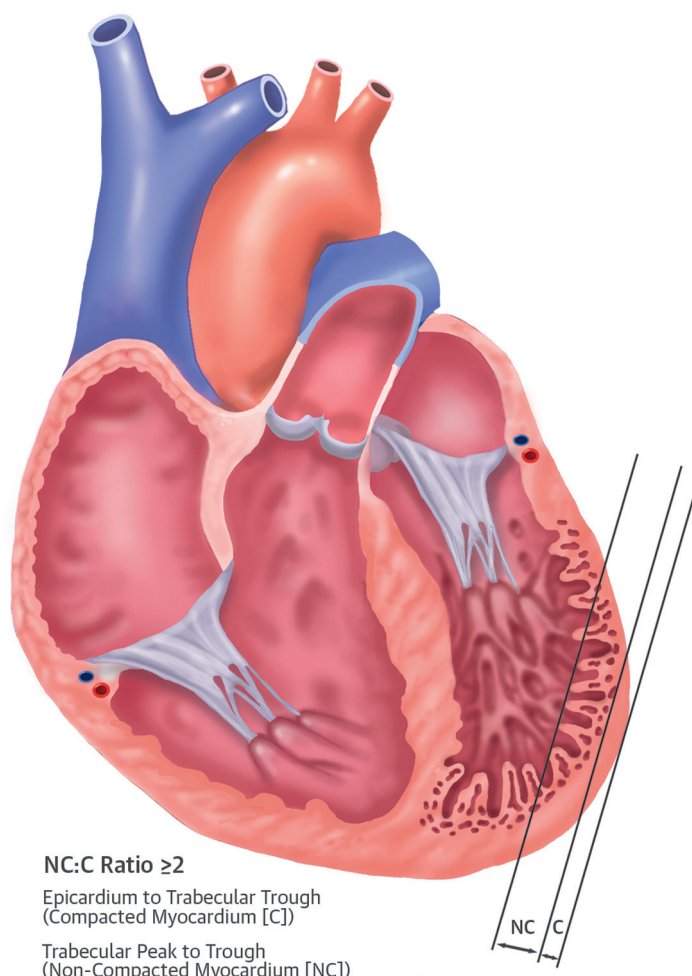
A study by Grothoff et al. (48) sought to establish quantitative CMR diagnostic criteria with good reproducibility that could differentiate noncompaction from other cardiomyopathies. The 4 basic criteria include:

1. Noncompacted LV myocardial mass >25%;
2. Total noncompacted LV myocardial mass index >15 g/m²;

3. Noncompacted/compacted myocardium ratio $\geq 3:1$ in at least 1 segment (1-3,7-16), excluding the apical segment (17); and
4. Trabeculation in segments 4 to 6 $\geq 2:1$ (non-compacted/compacted).

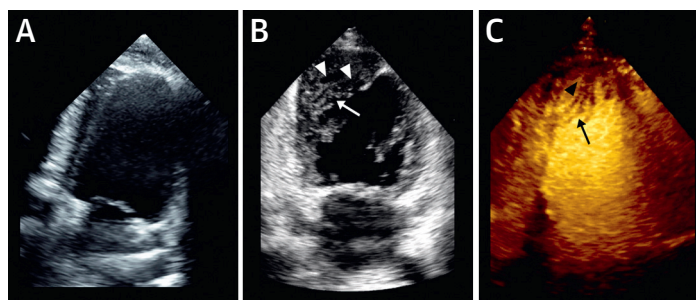
Although late gadolinium enhancement (LGE), a surrogate marker of myocardial fibrosis, was not identified in these patients, in previous studies, it was associated with the clinical features of non-compaction, including clinical symptoms, electrocardiographic abnormalities, and reduced ejection fraction (49-51).

CENTRAL ILLUSTRATION Isolated Noncompaction of the Left Ventricle in Adults: Compaction Ratio for Diagnosis of ILVNC



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Epicardium-to-trabecular-trough thickness is termed compacted myocardium (C), and trabecular-peak-to-trough thickness is termed noncompacted myocardium (NC). ILVNC = isolated left ventricular noncompaction.

FIGURE 1 Echocardiographic Images of Left Ventricular Noncompaction

Transapical views of the left ventricular apex in (A) a normal heart, (B) left ventricular noncompaction, and (C) left ventricular noncompaction with use of contrast echocardiography to better delineate the abnormal excess trabeculation (arrows) and inter-trabecular recesses (arrowheads).

Other imaging modalities that have been used for diagnosis of ILVNC include contrast ventriculography and computed tomography (52), although echocardiography and CMR appear to be the most helpful in clinical practice (39,45,53,54).

TREATMENT

In general, the management of patients with ILVNC remains similar to other cardiomyopathies and includes appropriate evidence-based heart failure treatments for left ventricular systolic dysfunction, appropriate management of arrhythmias, and consideration of oral anticoagulation to prevent mural thrombus formation. With this approach, there appears to be no significant difference in mortality compared with the other cardiomyopathies. In 1 series, the 3-year survival in patients with ILVNC was 85%, compared with 83% in patients with dilated cardiomyopathy (14). Deaths occurred in patients with decreased LV ejection fraction, suggesting that mortality likely relates more to left ventricular dysfunction than to the noncompaction itself (14,55). Timely initiation of renin-angiotensin-aldosterone inhibitors and beta-blockers, as well as appropriate device therapy (56,57), may prevent complications and improve survival, although randomized prospective data are not available in patients with ILVNC.

Ventricular tachyarrhythmias are a major contributor to mortality in ILVNC, occurring in more than 20% of patients. The risk of sudden cardiac death remains a major concern, particularly in patients with advanced disease, and suggests a major role for prophylactic implantable cardioverter-defibrillator (ICD) therapy. Kobza et al. (58) found that over a 3-year

follow-up, appropriate ICD discharge occurred in 25% and 50% of patients in whom a defibrillator was implanted for primary and secondary prevention, respectively (58). Supraventricular arrhythmias were also documented in a substantial number of these patients. These data should be carefully considered when deciding on the role for devices and their subsequent programming.

There is little to no data regarding the role of antiarrhythmic therapy in ILVNC. The current published data support early aggressive interventions, including defibrillator implantation and evaluation for transplantation, for patients with bundle branch block, increased left ventricular end-diastolic diameter, permanent or persistent atrial fibrillation, or NYHA functional class III or IV symptoms (8). Yearly Holter monitoring also appears to be essential in ILVNC to screen for asymptomatic arrhythmias.

Indications for ICD placement remain similar to other patients with dilated cardiomyopathy. For ILVNC specifically, current guidelines suggest that ICD therapy may be considered (Class IIB recommendation, Level of Evidence: C) (59). ILVNC patients presenting with syncope or symptomatic arrhythmias may benefit from electrophysiological study to assess for potentially inducible arrhythmias, but there are no available data to support the effect of ablative interventions in these patients.

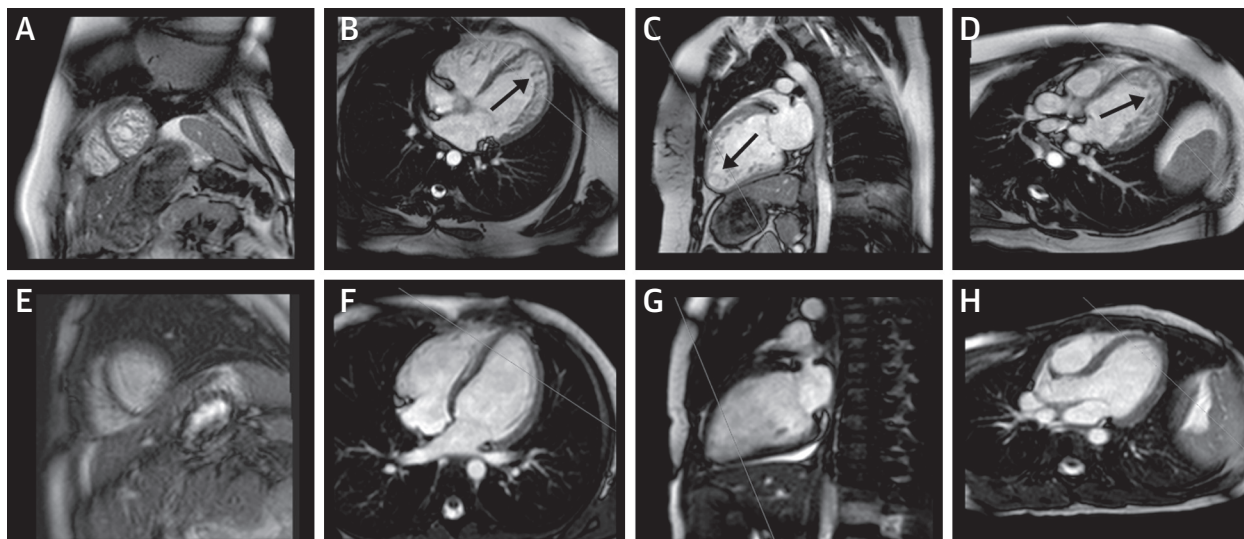
Another important aspect of treatment in ILVNC is the prevention of embolic complications. This is particularly true for patients with reduced ejection fraction (<40%), atrial fibrillation, or a history of thromboembolic complications. Some investigators recommend long-term prophylactic anticoagulation for all patients with ILVNC regardless of whether they have experienced thromboembolic complications (60) and irrespective of the degree of left ventricular dysfunction (3,8). However, anticoagulation should be approached in these patients with careful weighing of benefit and risk to identify those who will benefit most from this strategy.

TRANSPLANTATION

Factors in ILVNC that result in more rapid progression to transplantation or death include greater non-compaction/compaction ratios and location of involvement (greatest risk with apical involvement and lowest with mainly basal distribution) (61).

Patients with severe heart failure (NYHA functional class IIIB or IV) who have failed maximal medical/device therapy may be candidates for heart transplantation. According to Mancini et al. (62),

FIGURE 2 Cardiac Magnetic Resonance Images of Left Ventricular Noncompaction



Steady-state free precession imaging of left ventricular noncompaction (arrows) (A to D) compared with a normal heart (E to H) in short-axis, 4-chamber, vertical long-axis, and left ventricular outflow tract views, respectively.

patients with peak $\text{VO}_2 < 10$ ml/kg/min, a Seattle Heart Failure Model 1-year predicted survival score $< 80\%$, or medium/high risk Heart Failure Survival Score should be listed for transplantation. Due to poor outcomes with transplantation, patients presenting with cardiogenic shock requiring intravenous inotropes that cannot be tapered due to hypotension, end-organ damage, or symptoms should be palliatively managed (62).

PROGNOSIS

ILVNC is associated with considerable morbidity and mortality. In the Swiss cohort, 35% of the patients suffered early death, 53% required hospitalization for congestive heart failure, 41% had ventricular tachyarrhythmia, 12% required ICDs, and 12% required heart transplantation over 44 months of follow-up (8). The overall 5-year survival without heart transplantation was 58%. The high incidence of thromboembolic events (24%) and ventricular tachycardia (41%) in patients with impaired left ventricular function was a major contributor to mortality. In a prospective study of a sub-Saharan African population, sudden cardiac death was the most common cause of mortality (71.4%) in patients with ILVNC and heart failure (63).

More recent studies have reported substantially lower morbidity and mortality. Among 45 patients

referred to a cardiomyopathy center, survival free of transplantation was 97% over 4 years of follow-up (22). In another study, 46-month survival tracked closely with the presence of symptoms at presentation (69% vs. 100% when absent) (28).

The prognosis of patients with ILVNC has improved in recent years through earlier identification and application of heart failure medications and device therapy. Although few outcomes trials exist, in a recent study utilizing serial echocardiography, beta-blockers prevented the increase in left ventricular mass seen in the absence of therapy (64).

CONCLUSIONS

ILVNC is a rare cardiomyopathy associated with significant morbidity and mortality. It should be considered in the differential diagnosis of any patient with unexplained heart failure or arrhythmia. The classical clinical presentation is the triad of heart failure, arrhythmias, and embolic events.

Early diagnosis and treatment is associated with improved outcome, and screening asymptomatic relatives of affected patients via echocardiography appears important. Although echocardiography and CMR are the modalities of choice, contrast echocardiography, left-ventriculography, and computed tomography may also be considered.

Specific therapies have yet to be developed for ILVNC, and standard therapies available for other cardiomyopathies may be employed with relative success. Screening for arrhythmias and appropriate device implantation appears to be critical, as with other cardiomyopathies and low ejection fraction states. There also appears to be an important role for anticoagulation to prevent thromboembolic events.

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